Spruce budworm (*Choristoneura fumiferana*) antifeedants 4. Synthesis of specionin and biological studies

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Received April 25, 1994

ANMAR K. MOHAMMAD-ALI, T.H. CHAN, A.W. THOMAS, B. JEWETT, and G.M. STRUNZ. Can. J. Chem. **72**, 2137 (1994).

Specionin (**1**) was synthesized in seven steps from aucubin (**2**), an abundant iridoid form *aucuba japonica*. In a "no-choice" bioassay, specionin and several of its derivatives showed only modest antifeedant activity against the spruce budworm, while other derivatives were devoid of activity.

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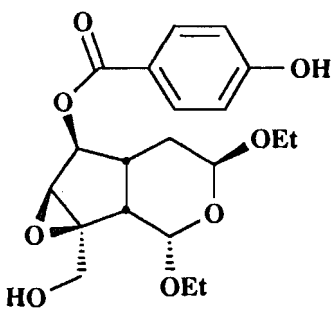
On a synthétisé la spécionine (**1**) en sept étapes à partir de l'aucubine (**2**), un iridoïde abondant de l'*aucuba japonica*. Dans un essai biologique sans choix, la spécionine et plusieurs de ses dérivés n'ont montré qu'une activité modeste comme antiappétent contre la tordeuse des bourgeons de l'épinette alors que d'autres dérivés n'ont aucune activité.

[Traduit par la rédaction]

Introduction

Because of problems associated with the widespread use of synthetic broad-spectrum pesticides, alternative strategies in the management of insect pests in forestry and agriculture are required. The spruce budworm, *Choristoneura fumiferana*, inflicts severe damage to the forest resource in Canada (1). A strategy that has been considered for the control of spruce budworm is to employ antifeedants to interfere with larval feeding behaviour (2–4). The approach offers the potential advantage that antifeedants could protect current year foliage while leading indirectly to budworm mortality without being generally toxic (5).

In screening programs using various insects, a number of natural products have been found to have antifeedant activity (6). Of particular interest to the spruce budworm problem is the report by Chang and Nakanishi that an active antifeedant compound, specionin (**1**), had been isolated from the leaves of *Catalpa speciosa* Warder (Bignoniaceae) (7, 8). Specionin was reported to be active at 50–100 ppm. Several chemical syntheses of **1** have since been reported (8–11) but without further biological studies. As part of our ongoing program in the chemical and biological studies of spruce budworm antifeedants (2–4, 12), we have undertaken the synthesis of specionin.



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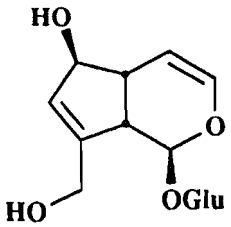

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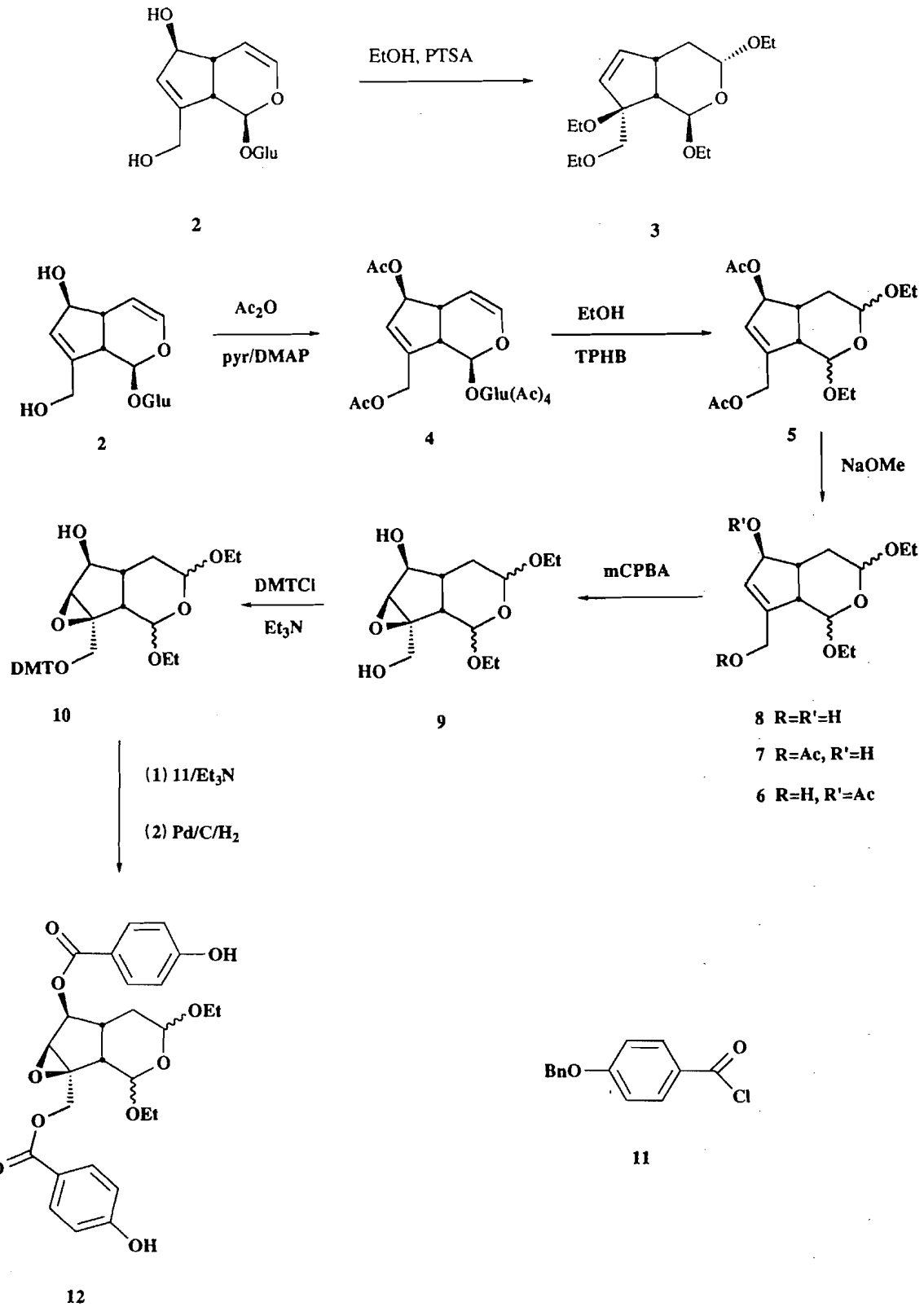
Chemical synthesis

Most previous syntheses of specionin have been designed to construct the iridoid skeleton through the oxidative cleavage of fused cyclopentenes (13), or retro-aldol cleavage of a 2 + 2 cycloadduct (14) or the Norrish type I cleavage of a norbornanone (8). Curran et al. (11), on the other hand, took advantage of an intramolecular cycloaddition of nitrile oxide onto a dihydropyran. All these were lengthy multistep syntheses and give low overall yield of the final, optically active, product. Alternatively, specionin could be synthesized from the iridoid natural product catapol (8).

We previously proposed (2) the use of the natural iridoid glycoside, aucubin (**2**), for the synthesis of specionin. Aucubin is present to the extent of about 1% of fresh plant weight in the leaves of *Aucuba japonica* (15) and can be extracted and purified in large quantities. It had been used as starting material for the synthesis of prostaglandins (16). However, aucubin is degraded extensively under the acidic conditions usually required for removal of the glycosidic linkage. Under the mildest ethanolysis conditions reported by us previously, aucubin rearranged to give **3** with migration of the double bond (2).

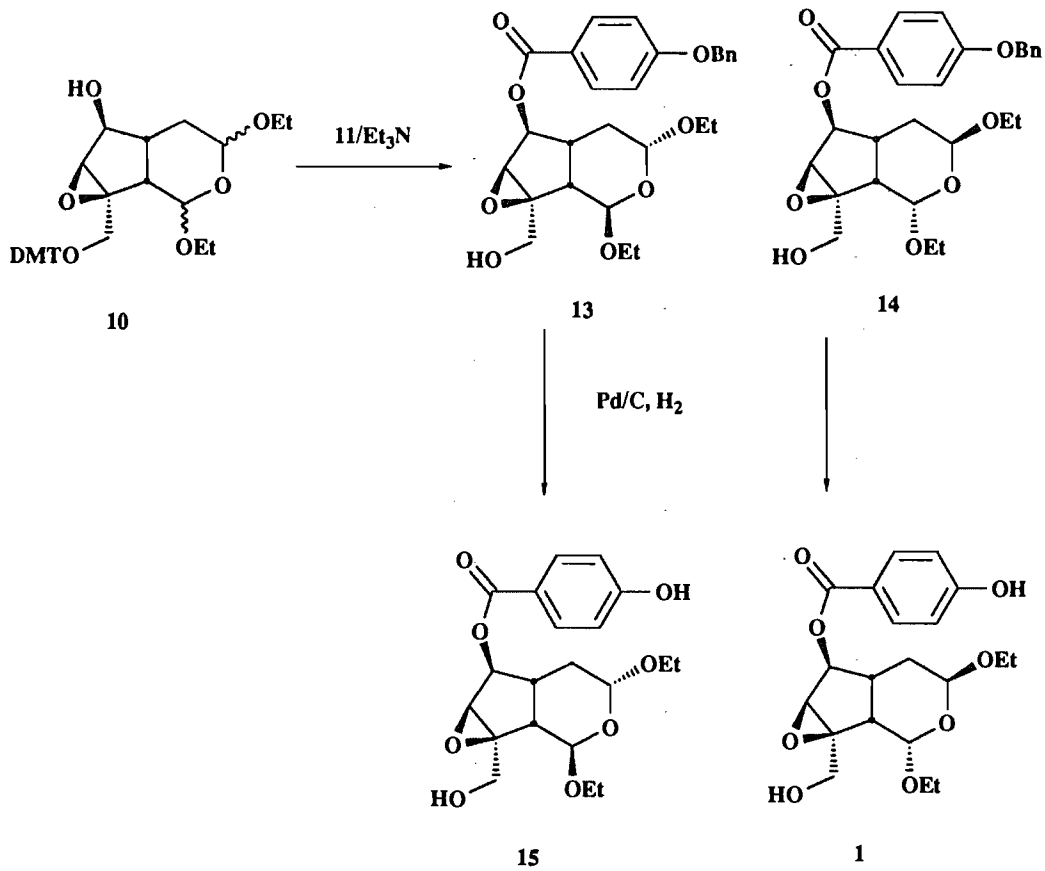
Recently, Falck and co-workers reported on the unique ability of triphenylphosphine hydrobromide (TPHB) to promote the addition of oxygen nucleophiles to glucals to give the corresponding acetals without the double bond rearrangement (Ferrier reaction) (17). On the basis of this report, we became interested in using TPHB for the ethanolysis of aucubin. Aucubin was first peracetylated with acetic anhydride in pyridine and dimethylaminopyridine (DMAP) to give **4** (Scheme 1). Ethanolysis of **4** with 20 mol% of TPHB in dichloromethane gave the bis-ethoxy acetal **5** in 60% yield. ^{1}H NMR showed clearly the removal of the sugar moiety and the addition of two ethoxy groups. However, ^{13}C NMR indicated the presence of four diastereomers arising from all possible configurations of the ethoxy groups. At this stage, we did not separate these isomers and proceeded with the synthesis using the mixture. Attempted epoxidation of **5** with *m*-chloroperbenzoic acid (mCPBA) was not successful. Accordingly, the acetate groups were cleaved with NaOMe to give a mixture of the monoacetates **6** and **7** and



SCHEME 1

the diol **8**, the ratio of which depended on reaction time. The three compounds could be separated by flash column chromatography. Allowing the reaction to proceed for sufficient time, the diol **8** was obtained as the major product in 69% yield. Epoxidation now of **8** with mCPBA afforded the β-epoxide **9** in 60% yield. The ^{1}H NMR spectral data of **9** were compared with those reported in the literature (8). This comparison indicated that in the mixture of stereoisomers constituting **9**, the second most abundant isomer had the same stereochemistry as that of (−)-specionin.

Before benzoylation of the C-6 hydroxyl group, the primary hydroxyl group had to be protected. The use of silicon protect-



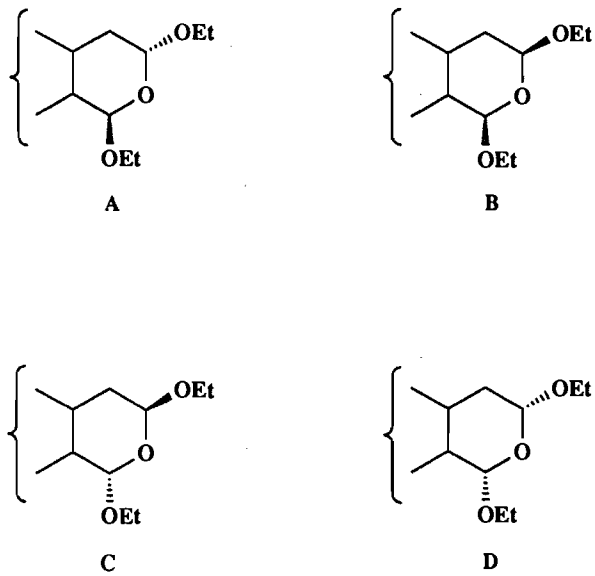
10 13 14 15 1

SCHEME 2

ing groups for this purpose has been reported but gave both the mono- and di-silylated compounds (8). We selectively protected the primary hydroxyl as its 4,4′-dimethoxytrityl (DMT) ether by reacting **9** with DMT chloride and triethylamine. The mono-DMT ether **10** was obtained in 75% yield. The coupling of **10** with an excess (4 equivalents) of *p*-benzyloxybenzoyl chloride (**11**) in the presence of triethylamine gave a product that, without purification, was treated with palladium hydroxide on carbon and cyclohexene to effect deprotection. To our surprise, the deprotected product, obtained in 60% yield, was clearly not specionin or any of its isomers. The material obtained was identified as the diester **12** (as a mixture of isomers) on the basis of ^{1}H and ^{13}C NMR and a HMQC experiment which indicated the coupling of the C-10 methylene protons with a carbonyl carbon. To explain the formation of **12**, it was assumed that the triethylamine hydrochloride formed was sufficiently acidic to remove the DMT protecting group. The unmasked primary hydroxy function was then benzoylated by the acid chloride.

The reaction was then repeated using less of the acid chloride **11** and for a shorter reaction time. Under these conditions, **13** and **14** were formed in a ratio of 3:1 in a combined yield of 55% (Scheme 2). The two diastereomers could be separated by column chromatography and were assigned the indicated stereochemistry. The minor isomer **14** was debenzylated over palladium on carbon with hydrogen to give pure (−)-specionin after silica gel column chromatography. Its proton NMR data were identical to the literature values (8). Similar debenzylation of the major isomer **13** gave the isomer of specionin, **15**, whose proton NMR was also identical with those reported in the literature (8).

Some comments need to be made regarding the difference in



SCHEME 3

stereoselectivity in the various syntheses of specionin reported in the literature. Obviously, the bis-ethoxy acetal structure can lead to four possible stereoisomers A, B, C, and D (Scheme 3). Structure C has the relative configuration corresponding to specionin. Previous syntheses of specionin that used *p*-toluenesulfonic acid (PTSA) for the ethanolysis step gave different diastereomeric mixtures. Vandewalle and co-workers reported a ratio of 4:4:1:1 for A, B, C, and D, respectively (8). In Hussain and Leonard's synthesis, A, B, and C were initially formed in

the ratio of 10:10:1, respectively, and D was not reported (9). Whitesell and Allen reported that only the C isomer was formed (10). Finally, Vandewalle, Leonard, and co-workers (8, 9) and Curran et al. (11) all reported that when the mixture of isomers of specionin was subjected to equilibration conditions ($BF_3.OEt_2$ or PTSA in EtOH), the ratio was changed in favour of specionin. The results of these equilibration reactions suggest that the stereochemistry of the bis-acetal in specionin is the thermodynamically stable arrangement. Nevertheless, it remains difficult to reconcile the different ratios of isomers produced under different reaction conditions. We suggest that the different ratios of diastereomeric mixtures reported could be due to the presence of different functionalities on the cyclopentane ring, particularly at the C-6 position. With intermediates where the cyclopentane (ene) ring has no substituent at C-6, as in Vandewalle's synthesis, or a hydroxy group at C-6, as in our synthesis, a mixture of all four diastereomers resulted, with the C arrangement being the minor isomer. In cases where the cyclopentane ring has the bulky *p*-hydroxy- or *p*-benzyloxybenzoate group present at C-6, then the specionin structure C predominated in the equilibration step, as in Leonard's, Whitesell's, or Curran's syntheses. A similar conclusion was recently drawn by Leonard and Hussain (9*b*). In our synthesis, even though specionin was obtained as the minor isomer, it is clear that the major isomer **15** could be equilibrated into specionin. Our synthesis represents therefore a seven-step sequence for the conversion of the readily available aucubin into specionin.

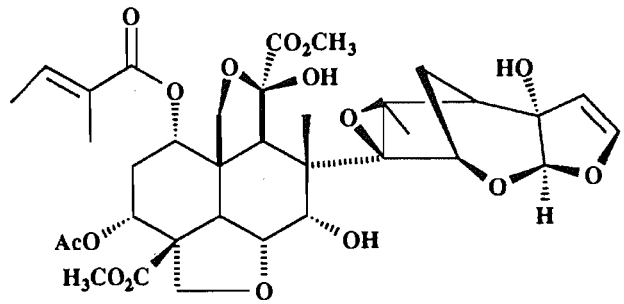
Biological studies

Many experimental designs have been devised to assess the antifeedant effect of a compound. These experiments generally fall into two broad classes, namely "choice" or "no-choice" assays. The occasional disparity between results reported for the efficacy of a given antifeedant compound, using different criteria and methodology, highlights the necessity to use care in designing a bioassay that will yield the most appropriate information for the system under investigation (18). A "choice" type of bioassay is appropriate for polyphagous insects that have access to several plant species. A "no-choice" test was preferred for spruce budworm larvae in the present study, as these larvae are oligophagous and alternate food sources are not usually available in the forest.

Diet containing between 0.023 and 0.60% wet weight of the test compounds was prepared by treating lyophilized artificial diet (19) with a solution of the compound, usually in methylene chloride, and then removing the solvent completely at 30°C on a rotatory evaporator. The residual powder was rehydrated to 80% water content with 0.4% aqueous potassium sorbate solution (fungicide). Control diets were treated as above with solvent alone, or were untreated. Newly emerged 2nd-instar larvae were reared individually on the diets (19) at 24°C, 17-h photoperiod, 25 replicates per test compound and control. After 17 days, the larvae were sacrificed and their mean development stage (i.e., mean instar) determined.

Specionin and a number of its derivatives were tested for antifeedant activity against the spruce budworm (Table 1). The result for each compound tested should be compared with that for the corresponding control. The biological assay showed that the development of larvae reared from 2nd instar on specionin (with 10% of **15** present) at 230 ppm was not significantly retarded from the control. Moreover, all the derivatives tested at 1500 ppm were found to be essentially inactive. Compounds **9** and **10** were moderately active when tested at 3000 ppm, and compound **8** was also moderately active when tested at 6000 ppm. These observations are in contrast to reported activity of specionin at 50 ppm (7). We must only attribute the difference to the type of bioassays used or to the possible presence of another active component in the leaf extract studied by Nakanishi.

These results should also be compared with the potent biological activity of azadirachtin (**16**) against spruce budworm



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Azadirachtin

larvae. In a similar "no-choice" bioassay, but starting with 3rd instars instead of 2nd instars, a concentration of 1.2 ppm of azadirachtin (in the form of 0.3% azadirachtin in Margosan-O, a commercial preparation of neem oil) stopped development (12). Future studies on the use of antifeedants for the control of spruce budworm should be directed at azadirachtin and related compounds (20).

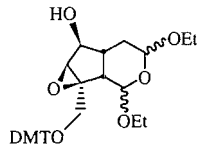
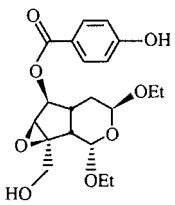
Experimental

General

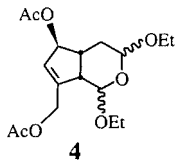
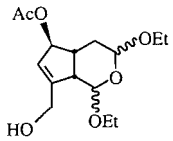
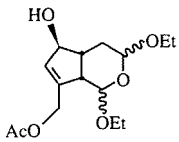
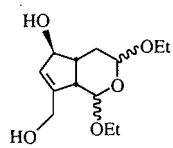
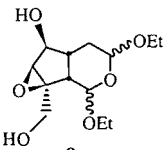
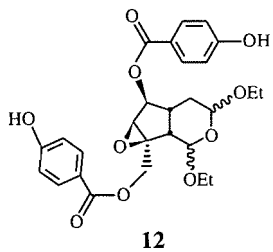
For all moisture-sensitive reactions, glassware was oven-dried at 200°C and cooled in a desiccator. All reactions were run under an argon atmosphere, dried by being passed through a column of indicating Drierite and potassium hydroxide, unless otherwise noted. Materials were obtained from commercial suppliers unless noted otherwise. Temperatures of reactions refer to bath temperatures. Solvents were dried as follows: tetrahydrofuran distilled from Na/benzophenone; hexane, pyridine, ethyl acetate, dichloromethane distilled from calcium hydride; methanol distilled from magnesium methoxide; triethylamine stored over sodium hydroxide pellets. Solvents were evaporated under reduced pressure using a Buchi rotary evaporator. Melting points (mp) were determined on a Gallenkamp block and were uncorrected. Flash column chromatography was performed using BDH Silica Gel 60 (230–400 mesh ASTM). Thin-layer chromatography was performed on commercial Merck silica gel 60 F_{254} precoated plates supplied by Merck Co. Visualization was effected by ultraviolet fluorescence (UV) or by spraying the plates with an anisaldehyde – sulfuric acid spray. Proton nuclear magnetic resonance (^1H NMR) spectra were taken on Varian XL-200, XL-300, XL-500, and JEOL 270 instruments. The data are reported in parts per million (ppm) relative to the TMS reference line with the multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad), coupling constants in hertz, and the number of protons also given for the major isomer in the cases of stereoisomeric mixtures. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian XL-300 (75.4 MHz) or JEOL-270 (67.8 MHz) instruments. Infrared (IR) spectra were obtained on an Analect AQS-18 FT-IR instrument and are reported in reciprocal centimeters (cm^{-1}). Solution spectra were obtained using sodium chloride cells of 0.2 mm thickness. Low- and high-resolution ammonia chemical ionization (CI) mass spectra were recorded on Hewlett–Packard 5980A and ZAB 2F HS instruments, respectively. Aucubin was generously provided by Dr. J.T. Edward of McGill University (15*b*).

TABLE 1. Biological assays of specionin and derivatives

(a)

Compound tested	Mean instar at concentrations 0.023%	0.30%
CH_2Cl_2 control	← 4.64 →	
 **10**		3.20[a]
 Specionin	4.24	

(b)

Compound tested	Mean instar at concentrations 0.15%	0.30%	0.60%
Nontreated control	← 5.28 →		
CH_2Cl_2 control	← 5.34 →		
 **4**	5.24	4.96	
 **6**	5.00		
 **7**	5.26		
 **8**	5.20	4.68	4.08[a]
 **9**	4.81	4.17[a]	
 **12**	5.12	5.15	

[a]Means significantly different from controls, $P < 0.05$.

Compound 4

To a suspension of aucubin (1.02 g, 3.0 mmol) in THF (20 mL), pyridine (1.5 mL, 18 mmol) was added. Acetic anhydride (1.6 mL, 18 mmol) was then added followed by the addition of a few crystals of 4-dimethylaminopyridine. The reaction mixture was stirred for 4 h at ambient temperature. The solution was diluted with ether and washed 3 times with 5% aqueous HCl solution, dried with magnesium sulfate, filtered, and evaporated under reduced pressure. The residue was then purified by flash column chromatography using hexane – ethyl acetate mixture, 1:1 ratio, to give **4** as a solid (1.56 g), mp 112–112.5°C, in 87% yield. FTIR ($CHCl_3$): 2960, 2259, 1755, 1660, 1432, 1371, 1231, 1045, 969, 911; ^{1}H NMR ($CDCl_3$): 6.16 (dd, J = 1.9 and 6.2 Hz, 1 H), 5.85 (bs, 1 H), 5.29 (bs, 1 H), 5.24 (t, J = 9.5 Hz, 1 H), 5.16 (d, J = 4.0 Hz, 1 H), 5.10 (t, J = 9.8 Hz, 1 H), 5.02 (dd, J = 8.1 and 9.6 Hz, 1 H), 4.91 (dd, J = 3.2 and 6.3 Hz, 1 H), 4.85 (d, J = 8.0 Hz, 1 H), 4.74 (bs, 2 H), 4.28 (dd, J = 4.5 and 12.3 Hz, 1 H), 4.15 (dd, J = 2.1 and 12.5 Hz, 1 H), 3.72 (ddd, J = 2.3, 2.4, and 9.9 Hz, 1 H), 3.19 (m, 1 H), 2.82 (m, 1 H), 2.1 (s, 3 H), 2.09 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H), 2.027 (s, 3 H), 2.01 (s, 3 H); ^{13}C NMR ($CDCl_3$): 170.6, 170.4, 170.2, 170.00, 169.2, 169.0, 144.3, 139.6, 127.1, 103.9, 95.8, 93.4, 82.3, 72.3, 71.9, 70.4, 68.1, 61.5, 61.1, 46.6, 39.00, 20.9, 20.6, 20.4; MS (CI): 616 (100, M + NH_4^+); HRMS calcd. for $C_{27}H_{38}N_1O_{15}$: 616.2241; found: 616.2244.

Compound 5

Triphenylphosphine hydrobromide (TPHB) (0.012 g, 0.037 mmol) was added to a dichloromethane solution of acetylated aucubin **4** (0.119 g, 0.185 mmol) and absolute ethanol (0.027 mL, 0.444 mmol). The mixture was refluxed overnight, then excess solvent was evaporated. The residue was redissolved in ether. The organic layer was washed with saturated aqueous sodium bicarbonate and brine, dried with magnesium sulfate, filtered, and evaporated under reduced pressure. The residue was then subjected to flash column chromatography using hexane – ethyl acetate (2:1) as the eluent to give **5** (anomeric mixture, 38 mg, 60% yield). FTIR ($CDCl_3$): 2979, 2932, 2362, 2263, 1733, 1450, 1376, 1242, 1106, 1022; ^{1}H NMR ($CDCl_3$): 5.80 (s, 1 H), 5.77 (s), 5.74 (s), 5.58 (m), 5.36 (bs, 1 H), 5.26 (bs), 4.95 (dd, J = 5.1 and 5.5 Hz, 1 H), 4.79 (dd, J = 4.9 and 4.7 Hz), 4.65 (bs, 2 H), 4.63 (d, J = 8.1 Hz, 1 H), 4.47 (d, J = 5.6 Hz), 4.2 (dd, J = 3.5 and 3.9 Hz), 3.84 (dq, J = 7.2 and 9.5 Hz, 2 H), 3.49 (dq, J = 7.2 and 9.5 Hz, 2 H), 3.23 (m), 3.16 (d, J = 9.0 Hz), 2.89 (t, J = 7.7 Hz, 1 H), 2.82 (t, J = 7 Hz), 2.65 (m), 2.56 (dd, J = 5.8 and 5.8 Hz), 2.46 (m, 1 H), 2.09 (s, 3 H), 2.02 (s, 3 H), 1.81 (m, 1 H), 1.52 (ddd, J = 6.8, 3.6, and 6.8 Hz, 1 H), 1.19 (dt, J = 7.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$): 15.1, 20.8, 21.2, 29.5, 29.6, 29.7, 30.6, 38.9, 39.8, 40.4, 41.0, 48.0, 48.1, 48.3, 49.2, 61.7, 61.9, 61.9, 62.5, 63.1, 63.2, 63.7, 63.8, 63.8, 64.4, 65.5, 82.4, 83.0, 84.0, 84.7, 95.3, 96.21, 96.8, 96.9, 97.4, 97.2, 97.5, 100.2, 125.5, 126.0, 127.2, 128.0, 128.8, 130.9, 143.2, 144.5, 145.0, 145.3, 170.4, 170.5, 170.5, 171.0, 171.0, 171.2; MS (CI): 360 (4, M + NH_4^+), 177 (35), 180 (35), 209 (58), 226 (73), 237 (100).

Compounds 6, 7, and 8

Sodium methoxide (0.07 g, 1.29 mmol) was added to a solution of **5** (0.20 g, 0.59 mmol) in dry methanol (5 mL). The mixture was stirred for 3 h at room temperature. The solution was filtered and evaporated under reduced pressure. The material was then subjected to flash column chromatography using hexane and ethyl acetate (3:1) as eluent to separate compounds **6**, **7**, and **8**. Compound **8** (anomeric mixture) was obtained as a colorless oil (0.10 g, 69% yield). FTIR ($CDCl_3$): 3470, 2978, 2929, 2244, 1710, 1438, 1418, 1361, 1223, 1117, 1092, 1038, 1007, 964, 940; ^{1}H NMR ($CDCl_3$): 5.78 (d, J = 1.0 Hz, 1 H), 5.74 (s),

5.29 (s), 5.01, (d, J = 4.9 Hz), 4.99 (dd, J = 4.9 and 5.5 Hz, 1 H), 4.74 (dd, J = 3.2 and 8.3 Hz), 4.66 (s, 1 H), 4.62 (d, J = 8.1 Hz, 1 H), 4.37 (d, J = 7.3 Hz), 4.21 (bs, 2 H), 3.94 (dq, J = 7.1 and 9.5 Hz, 1 H), 3.81 (dq, J = 7.1 and 9.6 Hz, 1 H), 3.50 (dq, J = 7.1 and 9.5 Hz, 2 H), 3.19 (m), 2.89 (t, J = 7.9 Hz, 1 H), 2.75 (t, J = 7.6 Hz), 2.44 (m), 2.33 (m, 1 H), 1.98 (m, 1 H), 1.81 (m, 2 H), 1.62 (dddd, J = 5.5, 5.6, and 5.6 Hz, 1 H), 1.23 (t, J = 7.1 Hz), 1.22 (t, J = 7.1 Hz, 6 H), 1.20 (t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$): 15.0, 15.1, 29.1, 29.6, 29.8, 44.1, 44.6, 46.4, 48.1, 48.6, 48.8, 60.9, 61.21, 61.5, 63.1, 64.0, 64.1, 64.4, 64.5, 80.2, 80.6, 81.28, 95.36, 97.09, 97.54, 97.64, 97.77, 101.36, 129.6, 130.5, 131.4, 146.5, 147.0, 147.2; MS (CI): 230 (16, M − C_2H_4), 167 (32), 184 (100), 195 (38), 213 (16).

Compound ***6*** (anomeric mixture). ^{1}H NMR ($CDCl_3$): 1.20 (t, J = 7.0 Hz, 3 H), 1.63 (dddd, J = 5.4, 5.6, 5.8, and 5.2 Hz), 1.8–2.0 (m, 2 H), 2.07 (s), 2.08 (s), 2.09 (s, 3 H), 2.29–2.41 (m, 1 H), 2.75 (t, J = 6.4 Hz), 2.81 (t, J = 7.7 Hz, 1 H), 3.09–3.10 (m), 3.25–3.20 (m), 3.43–3.53 (m, 2 H), 3.77–3.92 (m, 2 H), 4.40 (d, J = 6.1 Hz), 4.58 (d, J = 7.7 Hz), 4.65 (bs, 2 H), 4.67 (bs, 1 H), 4.99–4.93 (m, 2 H), 5.73 (s), 5.79 (s, 1 H); ^{13}C NMR ($CDCl_3$): 15.1, 20.8, 29.4, 29.5, 31.1, 42.0, 43.8, 44.6, 45.6, 47.9, 48.0, 48.3, 48.64, 62.1, 62.8, 63.1, 63.8, 64.0, 64.5, 80.2, 80.4, 81.8, 82.5, 95.6, 96.3, 97.2, 97.6, 100.8, 129.9, 130.5, 131.2, 132.3, 141.1, 142.5, 142.8, 170.6, 170.7.

Compound ***7*** (anomeric mixture). ^{1}H NMR ($CDCl_3$): 1.20 (t, J = 7.1 Hz, 3 H), 1.25 (t, J = 7.2 Hz, 3 H), 1.50 (dddd, J = 7.1, 2.9, 2.9, and 7.1 Hz, 1 H), 1.85–1.76 (m, 1 H), 2.01 (s, 3 H), 2.02 (s), 2.04 (s), 2.16–2.07 (m), 2.66–2.40 (m), 2.85 (t, J = 7.0 Hz), 2.99 (t, J = 8.0 Hz, 1 H), 3.23 (m), 3.57–3.46 (m, 2 H), 3.95–3.80 (m, 2 H), 4.22 (bs, 2 H), 4.44 (d, J = 6.8 Hz), 4.67 (d, J = 8.0 Hz, 1 H), 4.97 (m, 1 H), 5.34 (bs, 1 H), 5.49 (m), 5.59 (m), 5.72 (s), 5.75 (s, 1 H); ^{13}C NMR ($CDCl_3$): 15.0, 15.1, 21.2, 29.2, 29.9, 30.6, 39.5, 40.4, 41.6, 48.1, 48.3, 49.2, 54.9, 60.7, 61.1, 61.3, 63.1, 63.3, 63.8, 64.0, 64.3, 64.5, 82.5, 83.2, 83.6, 84.1, 95.2, 97.0, 97.3, 100.8, 124.8, 125.2, 126.4, 127.2, 148.9, 149.3, 149.9, 150.3, 171.0, 171.2.

Compound ***9***

mCPBA (0.18 g, 1.03 mmol) was added to a dichloromethane solution of **8** (0.13 g, 0.519 mmol). After 1 h at ambient temperature, an additional portion of mCPBA was added to the reaction mixture and stirring was maintained for 1 h at room temperature. Saturated aqueous sodium bicarbonate was added and the mixture was stirred for 30 min. The mixture was evaporated under vacuum and the material was then subjected to flash column chromatography, using hexane and ethyl acetate (1:3) as the solvent system to give **9** (anomeric mixture) as a colorless oil (0.082 g) in 58% yield. FTIR ($CDCl_3$): 3588, 2979, 2932, 2264, 1440, 1381, 1343, 1118, 1074, 1031, 970; ^{1}H NMR ($CDCl_3$): 4.99 (d, J = 3.9 Hz, 1 H), 4.96 (d, J = 3.2 Hz), 4.81 (dd, J = 2.7 and 7.0 Hz), 4.73 (dd, J = 3.5 and 9.0 Hz), 4.59 (d, J = 9.2 Hz, 1 H), 4.45 (dd, J = 8.5 and 1.0 Hz, 1 H), 4.13 (dd, J = 1.0 and 7.5 Hz), 4.04 (d, J = 13.4 Hz, 1 H), 4.00 (dd, J = 7.1 and 9.3 Hz), 3.95 (d, J = 12.6 Hz, 1 H), 3.82 (dq, J = 7.1 and 9.3 Hz, 1 H), 3.70 (dq, J = 7.1 and 9.6 Hz, 1 H), 3.68 (d, J = 12.5 Hz), 3.51 (d, J = 1.2 Hz), 3.47 (dq, J = 7.1 and 9.5 Hz, 1 H), 3.468 (d, J = 1.5 Hz, 1 H), 3.46 (dq, J = 7.1 and 9.5 Hz, 1 H), 2.69 (dd, J = 4.2 and 7.4 Hz, 1 H), 2.60 (dd, J = 3.3 and 8.5 Hz), 2.36 (dd, J = 7.0 and 9.0 Hz, 1 H), 1.97 (m, 3 H), 1.86 (m, 1 H), 1.27 (t, J = 7.1 Hz), 1.20 (t, J = 7.1 Hz, 3 H), 1.20 (t, J = 7.0 Hz), 1.18 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$): 98.2, 96.3, 93.8, 93.5, 77.1, 75.1, 72.2, 69.5, 66.4, 65.4, 64.5, 63.7, 63.2, 63.1, 62.7, 61.0, 60.6, 60.4, 53.7, 41.5, 40.1, 36.3, 36.2, 31.6, 29.1, 28.7, 26.3, 15.1, 15.0; MS (CI): 292 (10, M + NH_4^+), 229 (60), 246 (72), 279 (100).

Compound ***10***

4,4′-Dimethoxytrityl chloride (0.080 g, 0.23 mmol) was added to a solution of **9** (0.043 g, 0.15 mmol) in dichloromethane (3 mL). Excess triethylamine (0.15 mL) was added to the reaction mixture, which was then stirred overnight at room temperature. Toluene was added and the mixture was evaporated to dryness under reduced pressure. The material was then redissolved in ethyl acetate, washed with brine, dried with magnesium sulfate, filtered, and evaporated under reduced pressure. The product was then subjected to flash column chromatography using hexane – ethyl acetate in a ratio of 2:1, respectively, to give **10** (anomeric mixture) as a colorless oil (68.3 mg) in 75% yield. FTIR ($CDCl_3$): 3595, 2976, 2933, 2840, 2362, 2252, 1703, 1608, 1580, 1463, 1382, 1343, 1300, 1151, 1006, 974, 938, 898; ^{1}H NMR ($CDCl_3$): 0.81 (t, J = 7.1 Hz), 0.88 (t, J = 7.1 Hz), 1.17 (t, J = 7.1 Hz, 3 H), 1.21 (t, J = 7.1 Hz, 3 H), 1.22 (t, J = 7.1 Hz), 1.28 (t, J = 7.1 Hz), 1.72 (m, 1 H), 1.84 (m, 1 H), 1.95 (m, 1 H), 2.22 (t, J = 8.4 Hz, 1 H), 2.37 (dd, J = 7.5 and 9.2 Hz), 2.80 (m), 2.93 (m), 3.15 (d, J = 10.7 Hz), 3.25 (d, J = 11.8 Hz, 1 H), 3.32 (d, J = 7.5 Hz), 3.46 (m, 2 H), 3.63 (d, J = 11.5 Hz, 1 H), 3.69 (m, 2 H), 3.78 (s, 6 H), 3.79 (s), 3.82 (s), 3.85 (s, 1 H), 4.01 (m), 4.34 (d, J = 8.8 Hz, 1 H), 4.47 (bs, 1 H), 4.60 (d, J = 9.2 Hz), 4.68 (d, J = 4.1 Hz), 4.74 (dd, J = 2.3 and 7.8 Hz), 4.93 (d, J = 3.6 Hz, 1 H), 5.00 (d, J = 3.7 Hz), 6.83 (d, J = 8.9 Hz, 4H), 7.31 (m, 9H); ^{13}C NMR ($CDCl_3$): 158.5, 158.5, 144.9, 144.5, 136.24, 136.0, 136.0, 135.6, 130.1, 130.0, 128.2, 128.1, 127.8, 127.8, 126.8, 126.7, 113.2, 113.1, 113.1, 97.9, 96.9, 93.8, 93.2, 85.9, 85.7, 76.8, 75.6, 69.5, 65.1, 65.0, 63.9, 63.2, 62.6, 62.3, 62.1, 61.2, 60.4, 55.2, 53.8, 42.6, 40.1, 37.0, 36.6, 31.7, 29.3, 28.87, 26.6, 15.3, 15.1, 14.9, 14.8, 14.74; MS, FAB (glycerol) calcd. for $C_{34}H_{41}O_8$: 577.2801; found: 577.2804.

p-*Benzyloxybenzoyl chloride (****11****)*

To a stirred mixture of 4-benzyloxybenzaldehyde (1.14 g, 5.3 mmol) and magnesium sulfate (1.14 g) in acetone (30 mL) was added potassium permanganate (1.08 g, 2.1 mmol) over 2 h. The mixture was stirred at room temperature for an additional 30 min. The solvent was evaporated under reduced pressure and the solid residue was treated with 3 × 50 mL of hot water and filtered. The cold aqueous solution was washed with chloroform, then acidified with hydrochloric acid and extracted with chloroform. The organic layer was dried over magnesium sulfate, filtered, and evaporated under reduced pressure, to give 1.06 g of *p*-benzyloxybenzoic acid as white solid material, 88% yield, mp 167–168°C. FTIR ($CHCl_3$): 3073, 1690, 1605, 1254, 1240, 1168. MS (CI): 246(100, M + NH_4^+), 229(90, MH^+), 228(48, M + NH_4^+ − H_2O), 211(48). To a cold solution (0°C) of *p*-benzyloxybenzoic acid (0.13 g, 0.58 mmol) and oxalyl chloride (0.065 mL, 0.75 mmol) in dichloromethane (10 mL), a few drops of DMF were added and the solution was stirred for 2 h. The reaction mixture was evaporated under reduced pressure to give **11** (0.158 g) as white solid, mp 166–167°C (98% yield). FTIR ($CHCl_3$): 2263, 2240, 2226, 1771, 1739, 1601, 1262, 1210, 1165, 941. ^{1}H NMR ($CDCl_3$): 5.15 (s, 2 H), 7.03 (d, J = 9.0 Hz, 2 H), 7.40 (m, 5H), 8.08 (d, J = 9.0 Hz, 2 H); MS (CI): 248(19), 246(58, M + NH_4^+), 211(100).

Compound ***12***

To a solution of **10** (10 mg, 0.017 mmol) in dichoromethane (3 mL) was added triethylamine (0.009 mL, 0.068 mmol) and *p*-benzyloxybenzoyl chloride (**11**, 0.008 g, 0.034 mmol). After 48 h stirring at room temperature, a further equal amount of triethylamine and the acid chloride was added and the mixture was stirred for 24 h. A few drops of ethanol were then added and the mixture was diluted with diethyl ether, washed with saturated aqueous sodium bicarbonate and brine, dried with magnesium sulfate, filtered, and evaporated under reduced pressure. The product **12** (7.1 mg, 0.014 mmol) was then dissolved in ethanol (0.11 mL) and cyclohexene (0.057 mL), 20% palladium hydroxide on carbon (0.7 mg, 1:10 catalyst:substrate by weight) was added, and the suspension was stirred under reflux for 2 h. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The resulting material was then subjected to flash column chromatography using hexane – ethyl acetate (4:1) as the eluent to give **12** (anomeric mixture) as an oil in 60% yield. ^{1}H NMR ($CDCl_3$): 7.96 (d, J = 8.5 Hz, 2 H), 7.93 (d, J = 9.0 Hz, 2 H), 6.85 (d, J = 8.5 Hz, 2 H), 6.83 (d, J = 9.0 Hz, 2 H), 5.84 (bs, 2 H), 5.65 (d, J = 9.0 Hz, 1 H), 5.02 (d, J = 4.0 Hz, 1 H), 4.77 (d, J = 9.0 Hz, 1 H), 4.76 (d, J = 12.5 Hz, 1 H), 4.44 (d, J = 12.5 Hz, 1 H), 4.00–3.94 (dq, J = 7.0 and 9.0 Hz, 1 H), 3.88 (s, 1 H), 3.77–3.72 (dq, J = 7.0 and 9.0 Hz, 1 H), 3.55–3.45 (m, 2 H), 2.52 (d, J = 9.0 Hz, 1 H), 2.47 (dt, J = 7.0 Hz, 1 H), 1.88–1.78 (m, 2 H), 1.24 (t, J = 7.0 Hz, 3 H), 1.19 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$): 15.01, 15.03, 26.5, 32.9, 41.6, 58.7, 62.1, 63.3, 64.6, 77.4, 93.7, 97.9, 115.2, 115.3, 122.30, 122.32, 132.0, 132.2, 160.0, 160.1, 165.8, 166.5.

*Compounds **13** and **14***

To a solution of **10** (84 mg, 0.146 mmol) in dichloromethane (10 mL) was added triethylamine (0.082 mL, 0.58 mmol) and *p*-benzyloxybenzoyl chloride (0.072 g, 0.29 mmol). The mixture was stirred for 24 h. A few drops of ethanol were then added, the mixture was diluted with diethyl ether and washed with saturated aqueous sodium bicarbonate and brine, dried with magnesium sulfate, filtered, and evaporated under reduced pressure. The residue was then subjected to flash column chromatography using hexane – ethyl acetate (40:1) as eluent to give separately compounds **13** and **14** in a ratio of 3:1 in a combined yield of 55% (0.031 g).

*Compound **13***. ^{1}H NMR ($CDCl_3$): 8.01 (d, J = 9.0 Hz, 2 H), 7.41 (m, 5H), 6.99 (d, J = 9.0 Hz, 2 H), 5.57 (dd, J = 8.9 and 1.2 Hz, 1 H), 5.12 (s, 2 H), 5.01 (dd, J = 3.8 and 1.6 Hz, 1 H), 4.73 (d, J = 8.7 Hz, 1 H), 4.10 (d, J = 13.4 Hz, 1 H), 4.05 (dq, J = 7.1 and 9.3 Hz, 1 H), 3.77 (d, J = 1.2 Hz, 1 H), 3.74 (dq, J = 7.1 and 9.8 Hz, 1 H), 3.62 (d, J = 13.4 Hz, 1 H), 3.55 (dq, J = 7.1 and 9.3 Hz, 1 H), 3.48 (dq, J = 7.1 and 9.7 Hz, 1 H), 2.45 (m, 2 H), 1.82 (m, 2 H), 1.62 (bs, 1 H), 1.390 (t, J = 7.1 Hz, 3 H), 1.23 (t, J = 7.1 Hz, 3 H).

*Compound **14***. ^{1}H NMR ($CDCl_3$): 1.22 (t, J = 7.1 Hz, 3 H), 1.23 (t, J = 7.1 Hz, 3 H), 1.80 (m, 1 H), 2.0 (m, 1 H), 2.43 (d, J = 8.0 Hz, 1 H), 2.77 (dd, J = 8.5 and 3.9 Hz, 1 H), 3.46 (m, 1 H), 3.49 (m, 1 H), 3.70 (d, J = 1.3 Hz, 1 H), 3.74 (d, J = 12.3 Hz, 1 H), 3.82 (m, 1 H), 3.85 (m, 1 H), 3.98 (d, J = 12.3 Hz, 1 H), 4.71 (d, J = 9.2 Hz), 4.86 (dd, J = 2.6 and 6.5 Hz, 1 H), 4.94 (d, J = 4.6 Hz), 4.99 (d, J = 1.9 Hz), 5.03 (d, J = 3.9 Hz, 1 H), 5.11 (s, 2 H), 5.24 (m), 5.34 (dd, J = 1.3 and 7.9 Hz, 1 H), 5.55 (dd, J = 1.3 and 9.1 Hz), 6.97 (d, J = 9.2 Hz, 2 H), 7.40 (m, 5 H), 8.00 (d, J = 9.2 Hz, 2 H).

*Compound **15***

A mixture of **13** (7.0 mg; 0.014 mmol) and 10% palladium on carbon (5 mg) in ethanol (2 mL) was stirred under a hydrogen atmosphere for 3 h. The mixture was diluted with ethyl acetate, and filtered through Celite. The product was then subjected to flash column chromatography using ethyl acetate and hexane (4:6) as eluent to give **15** as a colorless oil (4.3 mg) in 78% yield. ^{1}H NMR ($CDCl_3$): 7.98 (d, J = 9.0 Hz, 2 H), 6.85 (d, J = 9.0 Hz, 2 H), 5.58 (dd, J = 1.0 and 8.7 Hz, 1 H), 5.30 (b, 1 H), 5.02 (dd, J = 1.5 and 4.5 Hz, 1 H), 4.73 (d, J = 8.5 Hz, 1 H), 4.10 (dd, J = 3.2 and 13.5 Hz, 1 H), 4.05 (dq, J = 7.0 and 9.0 Hz, 1 H), 3.78 (d, J = 1.0 Hz, 1 H), 3.74 (dq, J = 7.0 and 9.5 Hz, 1 H), 3.62 (dd, J = 11.0 and 13.5 Hz, 1 H), 3.55 (dq, J = 7.0 and 9.0 Hz, 1 H), 3.48 (dq, J = 7.0 and 9.5 Hz, 1 H), 2.52 (dd, J = 3.5 and 11.5 Hz, 1 H), 2.48–2.41 (m, 2 H), 1.85 (ddd, J = 3.5, 5.5, and 14.5 Hz, 1 H), 1.82 (dt, J = 1.5 and 14.5 Hz, 1 H), 1.30 (t, J = 7.0 Hz, 3 H), 1.23 (t, J = 7.0 Hz, 3 H); ^{13}H NMR ($CDCl_3$): 14.8, 14.9, 26.3, 32.6, 40.7, 58.0, 61.2, 63.2, 64.6, 65.2, 77.1, 93.6, 97.8, 115.0, 121.3, 132.0, 160.1, 166.1.

*Specionin (**1**)*

A mixture of **14** (3.0 mg, 0.006 mmol) and 10% palladium on carbon (2 mg) in ethanol (2 mL) was stirred under a hydrogen atmosphere for 3 h. The mixture was diluted with ethyl acetate, and filtered through Celite. The material was then subjected to flash column chromatography using ethyl acetate and hexane (4:6) as eluent to give **1** as a colorless oil (1.8 mg) in 79% yield. ^{1}H NMR ($CDCl_3$): 7.98 (d, J = 9.0 Hz, 2 H), 6.86 (d, J = 9.0 Hz, 2 H), 5.36 (dd, J = 8.5 and 1.5 Hz, 1 H), 5.06 (d, J = 4.0 Hz, 1 H), 4.88 (dd, J = 7.0 and 2.5 Hz, 1 H), 3.99 (d, J = 12.5 Hz, 1 H), 3.83 (m, 2 H), 3.77 (s, 1 H), 3.75 (d, J = 1.5 Hz, 1 H), 3.72 (d, J = 12.5 Hz, 1 H), 3.48 (m, 2 H), 2.78 (dd, J = 4.0 and 8.0 Hz, 1 H), 2.42 (m, J = 5.3, 8.0, and 8.5 Hz, 1 H), 1.99 (ddd, J = 2.5, 5.3, and 13.8 Hz, 1 H), 1.83 (dt, J = 7.0 and 13.8 Hz, 1 H), 1.24 (t, J = 7.0 Hz, 3 H), 1.20 (t, J = 7.0 Hz, 3 H).

Acknowledgement

Financial support from the Natural Sciences and Engineering Research Council of Canada (NSERC) and "le Fonds pour la formation de chercheurs et l'aide à la recherche (Québec)" (FCAR) is gratefully acknowledged.

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